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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,199	09/10/2003	Stephen M. Allen	BB1157USCNT	5569

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E I DU PONT DE NEMOURS AND COMPANY
LEGAL PATENT RECORDS CENTER
BARLEY MILL PLAZA 25/1128
4417 LANCASTER PIKE
WILMINGTON, DE 19805

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,199	ALLEN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 26-29 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The terminal disclaimer filed on 21 December 2005 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of 6,660,850 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. The incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f). The recitation of only the reference on the Clustal method of alignment on pg 9, lines 13-17 is improper because its recitation in the claims makes the material essential.

In the response filed 21 December 2005 Applicant urges that the material is not relied upon to overcome any objection, rejection, or other requirement imposed by the Office (response pg 3).

This is not found persuasive because the requirement was imposed in the prior Office action because recitation of the Clustal method of alignment in the claims makes the material essential.

5. The rejection of claims 26-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention is withdrawn in light of Applicant's amendment of claim 26.

6. The rejection of claims 26-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,660,850 is withdrawn in light of Applicant's filing a proper terminal disclaimer.

Claim Objections

7. Claim 26 is objected to because an article is missing before "Clustal" in line 6.

Claim Rejections - 35 USC § 112

8. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid encoding a SEQ ID NO:18 and constructs and vectors comprising them, does not reasonably provide enablement for nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 20 June 2005. Applicant's arguments filed 21 December 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them.

The instant specification, however, only provides guidance for cDNA libraries from a number of plants and plant tissues, including wheat developing kernel, and sequencing the inserts from an unknown number of the clones in these libraries (example 1), BLAST analysis of the cDNA sequences (example 2), identification of clones that have homology to the *Arabidopsis*, potato and corn brittle-1 homologs; the clones include SEQ ID NO:17, which encodes SEQ ID NO:18 (example 3). The specification also provides general guidance for the expression of chimeric genes in monocots (example 4), dicots (example 5), and microbes (example 6).

The instant specification fails to provide guidance for how to make or isolate nucleic acids encoding proteins with 90% identity to SEQ ID NO:18 - specific hybridization or PCR conditions, probes or primers are not recited. The instant specification fails to teach essential regions of the encoded protein. The instant specification also fails to provide guidance for how to use nucleic acids that encode proteins that have 90% identity to SEQ ID NO:18 but where the protein does not have adenylate translocator activity.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:18 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain adenylate translocator activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see

the abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

Given the unpredictability and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate Brittle-1-encoding nucleic acids encoding proteins with 90% identity to SEQ ID NO:18. Making all possible single amino acid substitutions in an 432 amino acid long protein like that encoded by SEQ ID NO:17 would require making and analyzing 19^{432} nucleic acids; these proteins would have 99.8% identity to SEQ ID NO:18. Because nucleic acids encoding proteins with 90% identity to SEQ ID NO:18 would encode proteins with 43 amino acid substitutions, many more than 19^{432} nucleic acids would need to be made and analyzed. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with 43 amino acid substitutions that also have adenylate translocator activity would require undue experimentation.

Assaying this nucleic acid requires plant transformation. Sullivan et al (1995, Planta 196:477-484) teach that the full-length maize Brittle-1 coding region could not be expressed in *E. coli* (pg 478, left column, paragraph 3), and an adenylate translocator requires an intact membrane for assaying. As the specification does not describe the transformation of any plant with a gene encoding proteins with 90% identity to SEQ ID NO:18, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with altered starch, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that there is a well-known correlation between *brittle-1* activity and protein structure. Applicant urges that Sullivan et al teaches the maize brittle-1 protein, which has a transit peptide, sequence similarity to mitochondrial inner envelope translocator proteins, and two membrane-spanning domains. Applicant also urges that Palmieri et al discloses a sequence motif present in mitochondrial carrier proteins. Applicant urges that Shannon et al teaches a ADP-Glc binding motif in the maize brittle-1 protein and that Patron et al discloses barley ADP-Glc transporter, but the Shannon motif is not present in this protein; Patron also teaches there are 4 transmembrane domains (response pg 3-5).

This is not found persuasive. Patron et al provides no teaching for the instant application, as it was published after the effective filing date for the full-length sequence (*i.e.*, after 1 March 2001). See *In re Glass*, 181 USPQ 31, 34 (CCPA 1974), which teaches that references published

after the filing date of an application may not be relied upon for the enablement of the specification. Furthermore, the specification does not overcome this by teaching the Patron motif. The Palmieri and Shannon motifs are discussed below.

Applicant urges that Appendix A shows an alignment of the instant, maize, and two barley brittle-1 proteins; the Palmieri and Shannon motifs are present and a consensus sequence is presented (response pg 5).

This is not found persuasive. The Shannon motif is not present in either the instant sequence or the barley sequences. As the barley sequences provide no teaching for the instant application, because they were published after the effective filing date of the instant application, the consensus sequence provides no teaching for the claimed nucleic acids. The Palmeiri motif only provides a teaching for a small portion (27 amino acids) of the 433 amino acid long overall sequence. Furthermore, the structural elements required for *brittle-1* function are not taught.

Applicant urges that Appendix B shows percent identity among the four proteins, Appendix C compares the hydropathic profiles of the wheat and maize sequences, and a website that calculates transmembrane helicies found 4-5 (response pg 5-6).

This is not found persuasive. The barley sequences provide no guidance, as discussed above. The structural elements required for *brittle-1* function are not taught in the specification. The cited websites could not be considered because they, and the version of them available at the effective filing date, were not sent.

Applicant urges that the proteins have chloroplast transit peptides (response pg 6-7).

This is not found persuasive because the transit peptide is only a portion of the protein, and the claimed nucleic acids encoding proteins with amino acid substitutions outside this region.

Applicant urges that the specification plus knowledge about *brittle-1* protein structure and activity provide specific guidance for making amino acid substitutions without undue experimentation. Applicant urges that the assay taught by Sullivan is routine (response pg 7).

This is not found persuasive. The full-length maize Brittle-1 coding region could not be expressed in *E. coli* (Sullivan et al, pg 478, left column, paragraph 3), and an adenylate translocator requires an intact membrane for assaying. Thus, screening of transformed plant to seed stage is required. Such screening requires undue experimentation in light of the lack of guidance in the specification as to which amino acid substitutions should be made.

9. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 20 June 2005. Applicant's arguments filed 21 December 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encoding proteins with 90% identity to SEQ ID NO:18 and that have any function. In contrast, the specification only describes a coding sequence from wheat that comprises SEQ ID NO:17. Applicant does not describe other nucleic acids encompassed by the claims, and the structural and functional features that distinguish all such nucleic acids from other nucleic acids are not provided.

No description is provided as to the function of the encoded protein.

Hence, Applicant has not, in fact, described nucleic acids that encode a protein with 90% identity to SEQ ID NO:18 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that in view of the foregoing one would understand the structure of proteins with 90% identity to SEQ ID NO:18 and having *brittle-1* activity (response pg 7).

This is not found persuasive because neither the specification nor the prior art describe no structures required for the *brittle-1* function; the Palmieri motif was not identified in the specification or the prior art as being part of *brittle-1* proteins and the Shannon motif is not present in SEQ ID NO:18. The level of skill and knowledge in the art at the time of filing was such that only one other brittle-1 protein was known.

Applicant urges that the specification discloses a representative number of sequences because it discloses that the invention encompasses more than the specific exemplary nucleotide and amino acid sequences (response pg 8).

This is not found persuasive because the structure of those variants is not described. The necessary and sufficient structural elements of a protein with *brittle-1* function are not described. One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species.

Conclusion

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne Kubelik, Ph.D.
February 28, 2006